essentially of the B domain, wherein said nucleotide mutation results in decreased sensitivity to a nucleoside analogue relative to an isolated wild type HBV.

33. (new) An isolated HBV mutant according to claim 32, comprising at least one mutation in a domain of the DNA polymerase consisting essentially of the B domain as defined in SEQ ID NO: 25.

34. (new) An isolated HBV mutant according to claim 32, comprising at least one mutation in a domain of the DNA polymerase consisting essentially of the B domain as defined in SEQ ID NO: 44.

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35. (new) An isolated HBV mutant, comprising a nucleotide mutation in a gene encoding a DNA polymerase or part thereof, wherein said mutation results in decreased sensitivity to a nucleoside analogue relative to a wild type HBV, said mutation resulting in at least one amino acid substitution in said DNA polymerase, the amino acid substitution being selected form the group consisting of Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Ile533Leu, Arg/Trp499Glu and Thr530Ser.

36. (new) An isolated mutant according to claim 32 or 35, wherein said nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.

37. (new) An isolated HBV mutant according to claim 32, comprising a mutant DNA polymerase having at least one amino acid selected from the group consisting of :

S/A HPI I/V LG$X_3$RK I/L PMG$X_5$GLS$X_6$F$LX_7$AQF$X_x$SA$X_8$ C/L S

wherein at least one of:

$X_3$ is L instead of F as in the wild type;

$X_5$ is L instead of V or G as in the wild type;

$X_6$ is L instead of P as in the wild type;

$X_7$ is M instead of L as in the wild type;

$X_x$ is S instead of T as in the wild type;

$X_8$ is L instead of I as in the wild type;

and wherein said mutant exhibits, relative to a wild type HBV, reduced sensitivity to a nucleoside analogue.

38. (new) An isolated HBV mutant according to claim 32, comprising a mutant DNA polymerase having at least one amino acid selected from the group consisting of :

Q/K T Y/F G $X_{19}$KLHL Y/L S/A HPI I/V LG$X_3$ RK I/L

PMG$X_5$GLS$X_6$F$LX_7$AQF$X_x$SA$X_8$ C/L S

wherein at least one of:

$X_{19}$ is E instead of R or W as in the wild type;

$X_3$ is L instead of F as in the wild type;

$X_5$ is L instead of V or G as in the wild type;

$X_6$ is L instead of P as in the wild type;

$X_7$ is M instead of L as in the wild type;

$X_x$ is S instead of T as in the wild type;

$X_8$ is L instead of I as in the wild type;

and wherein said mutant exhibits, relative to a wild type HBV, reduced sensitivity to a nucleoside analogue.

39. (new) An isolated mutant according to claim 37 or 38, wherein said nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.

40. (new) An isolated HBV mutant comprising at least one mutation in its genome wherein said at least one mutation produces at least one amino acid substitution in the DNA polymerase selected from the group consisting of Trp/Arg499Glu, Phe512Leu, Val519Leu and Ser559Thr, such that when said at least one amino acid substitution in the DNA polymerase is Phe512Leu, said mutant comprises at least a second mutation which produces at least one amino acid addition, substitution and/or deletion in said DNA polymerase; said mutant further comprising a mutation in the overlapping open reading frame of the HBV surface antigen.

41. (new) An isolated mutant according to claim 40, wherein said nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.

42. (new) An isolated HBV mutant according to claim 40, having the nucleotide sequence as set forth in SEQ ID NO:17, or a nucleotide sequence which is at least 60% similar to SEQ ID NO:17, wherein said mutant contains a Trp/Arg499Glu amino acid

substitution in the DNA polymerase and an Asp144Glu and Gly145Arg amino acid substitution in the surface antigen.

43. (new) An isolated HBV mutant according to claim 40 exhibiting, relative to an isolated wild type HBV, reduced sensitivity to a nucleoside analogue and reduced interactivity to an antibody to wild type HBV surface antigen, said HBV mutant comprising at least one of:

(i) a nucleotide sequence of its genome as set forth in SEQ ID NO:17 or a sequence having at least 60% similarity thereto;

(ii) a nucleotide sequence capable of hybridising to SEQ ID NO:17 under low stringency conditions at 42°C;

(iii) a mutation in an overlapping portion of open reading frames for DNA polymerase and HBV surface antigen; and

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(iv) a mutation in a region corresponding to amino acids 118 to 169 and/or 169 to 207 of HBV surface antigen,

wherein said mutant contains a Trp/Arg499Glu amino acid substitution in the DNA polymerase and an Asp144Glu and Gly145Arg amino acid substitution in the surface antigen.

44. (new) A method for determining the potential for an HBV to exhibit, relative to an isolated wild type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or

addition in a domain consisting essentially of the B domain of said DNA polymerase,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of lamivudine, penciclovir and famciclovir.

45. (new) A method for determining the potential for an HBV to exhibit, relative to an isolated wild type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in at least one of the B domain and the C domain of said DNA polymerase, wherein the screening detects at least one mutation selected from the group consisting of Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Ile533Leu, Met550Val, Met550Ile, Arg/Trp499Glu and Thr530Ser,

such that when said at least one amino substitution in the DNA polymerase is Met550Val, said method detects at least one amino acid substitution other than Leu526Met, and when said at least one amino acid substitution is Met550Ile, said method detects at least one amino acid substitution other than Phe512Leu or Val553Ile.

46. (new) A method for determining the potential for an HBV to exhibit, relative to an isolated wild type HBV, reduced sensitivity to at least one of penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in

at least one of the B domain and the C domain of said DNA polymerase, wherein the screening detects at least one mutation selected from the group consisting of Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Ile533Leu, Met550Val, Met550Ile, Arg/Trp499Glu and Thr530Ser,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of penciclovir and famciclovir.

47. (new) The method according to claim 45 or 46, wherein the screening for a mutation comprises sequencing said isolated HBV DNA or corresponding mRNA.

48. (new) The method according to claim 45 or 46, wherein the screening for a mutation comprises a PCR method or a PCR-based method.

49. (new) The method according to claim 45 or 46, wherein the screening for a mutation comprises a hybridization method.

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50. (new) An isolated *Hepadnavirus* mutant, comprising a nucleotide mutation in a gene encoding a DNA polymerase or part thereof, resulting in at least one amino acid addition, substitution and/or deletion in the part of said DNA polymerase consisting essentially of the B domain, wherein said nucleotide mutation results in decreased sensitivity to a nucleoside analogue relative to an isolated wild type *Hepadnavirus*.

51. (new) An isolated mutant according to claim 50, wherein the nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.